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Role of Prealbumin and Transferrin in Assessment of Malnutrition Risk in Pulmonary Tuberculosis Patients

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ABSTRACT

Malnutrition predisposes to TB and conversely TB can cause malnutrition. Thus, assessment of malnutrition risk is required in TB patients for their early recovery, prevention of relapse and enhance survival. Along with standard Arthropometric indices like Body Mass Index etc. these days visceral proteins Prealbumin (PAB) and Transferrin (TRA) are emerging as popular markers of nutritional status in pathological conditions since they are easy to estimate, standardized and influence morbidity and mortality. OBJECTIVE: Our objective is to assess nutritional status in terms of PAB and TRA level using Malnutrition Universal Screening Tool (MUST) as reference method and compare them with normal controls. METHOD: 55 controls and 70 PTB patients were enrolled for the study. Detailed history of weight loss and recent nutrient intake were noted for each patients and MUST score worked out. Albumin, Prealbumin, Transferrin and Cholesterol were estimated in serum samples. RESULTS: The present study showed significant ($p< 0.001$) decrease in Albumin, PAB, TRA and Cholesterol level in PTB patients. Also we found strong negative correlation of PAB and TRA ($r= -0.92$ and -0.84 respectively) with MUST score. MUST score >2 indicates severe risk of malnutrition in PTB patients. DISCUSSION: Decrease level of visceral protein is explained by acute phase response accompanying decrease synthesis and enhanced degradation of Negative acute phase protein during systemic inflammation as seen in PTB. Low dietary intake due to anorexia and pre-exsisting undernutrion also cause decrease in PAB and TRA level ($p<0.001$). Due to its short half life and rapid response to protein intake, PAB correctly indicates patients risk of malnutrition and to identify those requiring immediate nutritional intervention. CONCLUSION: Our results proposes that Biochemical Nutritional markers PAB and TRA should be made part of detailed nutrition protocol to monitor dietary regime of PTB patients.

KEYWORDS Prealbumin, Transferrin, Malnutrition, Pulmonary Tuberculosis.

SUMMARY

Pulmonary Tuberculosis (PTB) is an infectious global disease widely associated to malnutrition in a direct relationship that forms a vicious circle such that any decline in immune status due to malnutrition increases susceptibility to PTB while MTB infection leading to enhanced catabolism and anorexia causes malnutrition. Identifying malnutrition risk in PTB patients is of utmost importance to enhance their early recovery and prevent risk of relapse. The study deals with utility of visceral protein Prealbumin (PAB) and Transferrin (TRA) in assessment of malnutrition risk using "Malnutrition Universal Risk Tool" (MUST) as reference method. MUST is considered established reliable screening tool to identify PTB patients at risk of malnutrition and associated with mortality and morbidity. It considers patient's nutrient intake for past 5 days and weight loss in preceding 3-6 months in calculation of MUST score. Score of 2 or more indicates severe malnutrition risk. Serum PAB and TRA were estimated by immunoturbidimetric method in all subjects. PAB has short half life, small body pool and shows rapid response to changes in protein level, hence can be used in nutritional evaluation. Albumin, PAB and TRA were found to be significantly reduced in PTB patients (N=70) than healthy Controls (N=55) due to acute phase response, reduced hepatic synthesis, anorexia and pre existing undernutrition. PAB and TRA were negatively and strongly correlated to MUST score ($r=-0.92$ & -0.84 respectively) indicating corresponding decrease in PAB and TRA level with Risk of malnutrition. The study directs utility of PAB and TRA in nutritional evaluation in inflammatory condition wherein patients requiring nutritional intervention can be identified. However, direct relationship of this visceral protein with disease severity or outcome requires large scale studies.

INTRODUCTION

Pulmonary Tuberculosis (PTB) is a deadly infectious disease caused by different strains of Mycobacterium tuberculosis. One third of the world's population is infected with MTB, 9 million of these develop TB and almost 2 million die of this disease with new infections occurring in 1% of population each year (1). PTB is associated with poverty , overcrowding, alcoholism, drug addiction and malnutrition. The later is the most widely prevalent risk factor accounting for highest population attributable to TB, specially in India (2). India is the highest TB burden country with WHO statistic for 2011 gives an estimated figure of 2.2 million cases out of global incidence of 8.7 million cases (3). Malnutrition and Tuberculosis show cause effect relationship such that a decline in immune response due to nutritional deficiency, ageing, alcohol or drug abuse may lead to active TB while MTB infection causes loss of appetite and cachexia leads to malnutrition. studies have detailed the poor nutritional status in patients with TB measured in terms of Body Mass Index (BMI) , Mid upper arm circumference and skin fold thickness (4). Further, Acute Phase response (APR) induces catabolism and through a cascade of reactions causes reduction in level of certain visceral proteins i.e. Albumin. Prealbumin(PAB) and Transferrin(TRA) (5). Such visceral proteins that also act as inflammatory biomarkers have gained significance in assessment of nutritional status

in diseased. This study highlight the role of acute phase proteins- Prealbumin and Transferrin in nutritional assessment in patients with PTB.

MUST (Malnutrition Universal Screening Tool) is a simple, quick, valid and reliable tool of assessment of malnutritional risk in PTB patients and is associated with enhanced morbidity and mortality and used as reference method in this study(6). Prealbumin , also called Transthyretin has half life of approximately 1.9 days , much shorter than albumin (20 days) and is therefore more sensitive to changes in protein energy states and its concentration reflects recent dietary intake (7). It is thus assumed that PAB and TRA determination can be a simple, cost effective tool which can be easily standarised in clinical practice to identify malnourishment in hospitalized patients.

AIM : The aim of this study is to determine the level of visceral proteins , Prealbumin and Transferrin in PTB patients and establish their role as nutritional indicators to ascertain malnutrition risk in these patients.

MATERIAL AND METHOD: The study was conducted in Department of Biochemistry, SMS Medical College, Jaipur in collaboration with Institute of Respiratory Diseases (IRD). 70 adult patients diagnosed with Pulmonary Tuberculosis (Newly diagnosed and relapsed) were recruited that form Group B and 55 age matched healthy individuals tested free of MTB , without any previous or present symptoms of TB or any other pulmonary disease and non family members of patients served as controls (Group A). Patients suffering from drug resistant TB (MDR), extrapulmonary TB, those with significant renal, cardiac, neoplasm or respiratory disease (other than PTB like lung cancer) etc., diabetes, endocrine or genetic disorder were excluded from the study. HIV positive cases, Pregnant or lactating women and those on oral nutritional supplements were also excluded. All subjects gave their written consent to participate in the study. Data such as weight loss in preceding 3-6 months, nutritional intake for last 5 days, present weight, height and MUAC were obtained for each patients.

Determination of Visceral proteins:
Serum was used for analysis of plasma proteins. Total protein (Biuret method), Albumin (BCG method) and total Cholesterol (Cholesterol oxidase- Peroxidase method) were analyzed on autoanalyzer (Randox, imola3). Prealbumin and Transferrin were estimated by immunoturbidimetric method on autoanalyzer EM-360. Following methods were used for nutritional assessment:

1. MUST: It includes 3 variables i e. unintentional weight loss in preceding 3-6 months (weight loss<5% = 0, 5-40 % = 1 and > 10 % = 2), BMI (BMI >20.0= 0, BMI 18.5-20.0 =1, BMI < 18.5 = 2) and acute disease effect score (Add a score of 2 if there has been or is likely to be nutritional intake for > 5 days). Each is scored on a scale of 0,1 or 2 and their sum categories the malnutrition risk as low (0), medium (1) and high risk (≥2).
2. Body Mass Index: BMI < 16 was considered severe malnutrition, BMI = 16-18.5 was mild malnutrition and BMI = 18.5-24.9 were normal (8).
3. Prealbumin (PAB) and Transferrin (TRA) were assessed according to following proposed criteria. Patients classified into three classes i) Normal (PAB >15.0 mg/dl , TRA >150.0 mg/dl) ii) Mild Malnutrition (PAB = 9.0-15.0 mg/dl, TRA 101-149 mg/dl) and iii) Severe Malnutrition (PAB < 9.0 mg/dl, TRA <100.0 mg/dl) (9).
4. Total Cholesterol< 70.0 mg/dl was taken as severe malnutrition, Cholesterol = 70 – 140 mg/dl was considered as mild malnutrition while values > 140 mg/dl were taken as normal cholesterol.

Statistical Analysis: Data was presented as Mean ± SD. Correlation analysis was performed using pearson test. Comparison among groups was done by student t- test with $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION : Malnutrition is a clinical condition characterized by depletion in muscle mass/ body fat, associated with increased morbidity and mortality as observed in various wasting diseases like PTB well documented in many studies (10) and once again seen here. General characterstics of study population is summarized in table 1. Out of total 55 group A (Control) subjects, 63.6% were males and 36.4% females whose average age was 40.5± 15.88 years. 70 PTB patients (Group B) constitute 74.2% males and 25.7% females and with average age 44.5 ± 17.6 years. Significant difference was seen in BMI, MUAC, serum protein, albumin and cholesterol level between two groups (table 1.) ($p< 0.05$).

TABLE 1 : General characterstics and biochemical profile of study population.

	Group A (Healthy controls)		Group B (PTB cases)		Significance
No. of cases	N= 55		N= 70		
No. males	35 (63.6)		52 (74.2)		
No. females	20 (36.4)		18 (25.7)		
	MEAN ± S.D.	AT 95 % CI	**MEAN ± S.D.**	AT 95 % CI	
Average age in years	40.5± 15.88	36.2-44.8	44.5 ± 17.6	40.3-48.8	0.18 NS
BMI (Kg/m2)	22.2 ± 3.08	21.4-23	16.46 ± 3.1	15.7-17.2	< 0.001 S
MUAC (in mm)	259.5 ± 50.4	245.5-273.1	175.8 ± 19.0	171.2-180.3	< 0.001 S
SPUTUM STATUS					
NEGATIVE	55 (100)	-	29	-	< 0.001 S
+ 1	0 (0)	-	19	-	
+2	0 (0)	-	12	-	
+3	0 (0)	-	10	-	
S. PROTEIN (g/dl)	7.7 ± 0.8	7.52-7.98	6.4 ± 0.6	6.32-6.61	< 0.001 S
S. ALBUMIN (g/dl)	4.4 ± 0.7	4.17-4.56	2.8 ± 0.6	2.75-3.03	< 0.001 S
S. CHOLESTEROL (mg/dl)	189.5 ± 60.2	173.3-205.8	124.2 ± 29.4	117.2-131.0	< 0.001 S
S. PREALBUMIN (mg/dl)	22.3 ± 8.7	19.9-24.6	14.5 ± 6.0	13.1-16.0	< 0.001 S
S. TRANSFERRIN (mg/dl)	155.6 ± 59.0	139.5-171.7	119.7 ± 35.5	111.2-128.2	< 0.001 S
S. GLOBULIN (g/dl)	3.4 ± 0.61	3.2-3.5	3.57 ± 0.61	3.4-3.7	0.08 NS
ESR (mm Hg)	29.6 ± 13.2	26.0-33.1	48.3 ± 17.3	44.2-52.4	< 0.001 S

Values are in Mean ± SD. SD Standard deviation

Severe chacexia, increased body catabolism, anorexia beside low economic status with pre-exsisting malnutrition are key factors causing low level of protein in PTB patients. Albumin is a component of plasma antioxidant activity and negative APP that decreases in any inflammatory condition, injury or stress. Leakage through vascular endothelium and reduced hepatic synthesis may explain decreased level as observed in our study. Similarly Total cholesterol in PTB is significantly ($p < 0.001$) reduced than control group (Table 1) due to reduced intake, lipid peroxidation and enhanced lipid catabolic rate associated with TB (11). Prealbumin (PAB) is a plasma protein synthesized by hepatocytes & Its concentration closely reflects recent dietary protein intake (12). Both PAB and TRA not only shape physiological response to infection but also affect morbidity and mortality of disease and hence studied here. In our study, PAB and TRA were significantly low in PTB patients (14.5 ± 6.0 and 119.7 ± 35.5 mg/dl) than control group (22.3 ± 8.7 and 155.6 ± 59.0 mg/dl) respectively ($p<0.001$).

PTB is a chronic inflammatory disease that elicit T cell response and with increased level of cytokines that down regulates negative acute phase proteins including Albumin, Prealbumin and Transferrin. Further, low serum PAB and TRANS can be explained by acute hemodynamic changes occurring in response to tissue damage in PTB. All these factors along with pre-exsisting malnutrition, reduced hepatic synthesis, trans endothelial escape and anorexia are responsible for lower PAB and TRA in cases than controls. Various large scale studies show reduced PAB level in Tuberculosis cases (n=320) than in lung cancer cases (n=320) or healthy individuals (n=120). 75% of PTB, 31 % of lung cancer patients and only 6.7% of healthy individuals have reduced PAB level I e <170mg/l (12). It was also seen that PAB tends to normalize after 9 months of ATT but remain at lower level in drug resistance or TB relapse. The above fact highlight the potential role of PAB in differential diagnosis of lung cancer and monitoring therapeutic effect of TB drugs on PTB patients (12). Similarly TRA has been found to correlate with acute inflammation with a concomitant decrease in Newly diagnosed PTB patients (218 ± 54.7 mg/dl) as compared to on drug (244.6 ±61.1 mg/dl) and healthy control (270.4±22.8 mg/dl) in another study (13). These visceral protein can be an objective markers in monitoring disease improvement in TB. Some even suggest decrease in concentration of Transferrin correlated with severity of PTB or degree of inflammation (14). Thus, while utilizing these protein in nutritional assessment , various non nutritional factors like biological variations, hydration state, hepatic or renal failure and APR need to be considered.

Role of Visceral proteins in nutritional assessment

TABLE 2 : Outcome in relation to different methods of nutritional assessment.

NUTRITIONAL ASSESSMENT	GROUP A	GROUP B (PTB CASES) N= 70	P value
MUST			<0.001
Normal (score 0)	55 (100)	3 (4.3)	
Mild malnutrition (score 1)	0 (0)	2 (2.86)	
Severe malnutrition (score 2 or more than 2)	0 (0)	65 (92.8)	
BMI			<0.001
Normal (18.5-24.5)	49 (89.1)	21 (30.0)	
Mild malnutrition (16-18.5)	6 (10.9)	16 (22.8)	
Severe malnutrition (< 16.0)	0 (0.00)	33 (47.2)	
PREALBUMIN			<0.001
Normal (>15.0 mg/dl)	38(69.0)	17 (24.3)	
Mild malnutrition (9.0-15.0 mg/dl)	14(25.45)	28 (40.0)	
Severe malnutrition (< 9.0 mg/dl)	3 (5.45)	25 (35.7)	
TRANSFERRIN			<0.001
Normal (>150.0 mg/dl)	30 (54.5)	15 (21.4)	
Mild malnutrition (101.0-149.0 mg/dl)	15 (27.3)	35 (50.0)	
Severe malnutrition (<100.0 mg/dl)	10(18.2)	20(28.6)	
CHOLESTEROL			<0.001
Normal (>140.0 mg/dl)	45 (81.8)	20 (28.57)	
Mild malnutrition (70.0-140.0 mg/dl)	10 (18.2)	48(68.6)	
Severe malnutrition (<70.0 mg/dl)	0 (0.00)	2 (2.86)	
Albumin			<0.001
Normal (3.1-5.2 g/dl)	54 (98.2)	31 (44.3)	
Malnutrition (<3.0 g/dl)	1(1.8)	39 (55.7)	

Values are numbers and values in parenthesis are percent.

TABLE 3. Prevalence of malnutrition assessed by different methods in 70 PTB patients

	GROUP A (CONTROLS) N=55			GROUP B (PTB PATIENTS) N=70		
METHOD		mild	severe	normal (%)	mild	severe
1.MUST	100	0	0	4	3	93
2.BMI	89	11	0	30	23	47
3.PREALBUMIN	69	25	6	24	40	36
4. TRANSFERRIN	55	27	18	21	50	29
5. ALBUMIN	98	2		44	56	

Among various methods of nutritional assessment, both anthropometric (BMI) and Biochemical indices are used. BMI is a statistical measure of a weight of a person scaled according to height (15). It does not considers clinical and biochemical alterations during acute illness. Although weight loss and chachexia occurs primarily to MTB infection which directly affects BMI, making it significant indicator of malnutrition risk in acute infection, but lacks specificity. MUST (Malnutrition Universal Screening Tool) is a well documented screening tool for nutritional assessment in PTB patients. The method has predictive validity with regard to mortality and length of hospital stay particularly in patients with PTB and thus is a useful prognostic indicator of survival of hospitalized patients (16) and hence was used as reference method in this study.

Table 4: Mean value of nutritional parameters in relation to MUST score in patients Group

MUST Score N=70	0 N=3	1 N=2	2 N=13	3 N=16	4 N=13	5 N=8	6 N=15	Correlation coefficient r
BMI (Kg/m2)	20.56	16.41	15.28	15.02	18.06	15.12	16.08	-0.504
ALBUMIN (g/dl)	4.6	3.36	3.10	2.76	2.48	2.60	2.86	-0.786
PREALBUMIN (mg/dl)	20.42	18.62	17.92	11.25	12.08	11.65	10.2	-0.922
TRANSFERRIN(mg/dl)	161.4	117.2	111.6	96.7	100.14	103.12	91.85	-0.840
CHOLESTEROL (mg/dl)	136.5	112.0	129.4	116.3	109.87	96.33	121.66	-0.554

For each method, percentage of patients in each category is given in **table 3.** Data showed that using PAB and TRA as nutritional indicators, 76% and 79% of patients show varying degree of malnutrition is in agreement with available literature (17) while

only 56% were classified malnourished using albumin alone. This can be explained by the fact that decrease or increase in albumin is affected by number of factors apart from inflammation and dietary intake such as Dehydration , old age, and APR decreases albumin level. Very high percent (93 %) were severely malnourished using MUST method since it takes into account clinical and dietary factors associated with TB. Our Data (**Table 4**) also showed strong negative correlation of PAB and TRA with MUST score (r= -0.92 and -0.84 respectively). MUST score more than 2 suggest high risk of malnutrition. This suggest high significance of PAB and Trans to detect risk of malnutrition and hence mortality risk in PTB. Since MUST method utilize recent nutrition deprivation in patients (for >5 days) as one of its scoring parameter, PAB that is affected by recent dietary intake show rapid decrease responsible for strong correlation. Such rapid changes accompanying acute illness has been observed by other researchers as well for example, a decrease of upto 50% in PAB is expected after a few days of inadequate intake and /or disease with an APR, a condition that often coexsist in severely ill patients. Conversely, a rapid increase in PAB is seen when adequate nutrition was restored or CRP stabilized (17), Hence PAB is now emerging better indicator of malnutrition even in pathological condition since it changes rapidly in response to nutritional support. Further , taking MUST as reference method and combining severe and mild malnutrition into single group, sensitivity and specificity were obtained for each method. All methods show 100% Specificity , means that all can truly detect malnutrition in an individual. TRA and PAB show good sensitivity i.e. 82% and 79% respectively as compared to albumin i.e. 58%. BMI method was 73.1 % sensitive in comparison to MUST in detecting malnutrition . Though BMI is simply dependent on weight in relation to height, it assumes significance in PTB and other such wasting disorders that causes chacexia and increased body catabolism leading to observable weight loss. in a study PAB was found to correlate significantly with DNA (Detailed Nutritional Assessment) method in detecting PEM with and without increased CRP (>5.0mg/L), indicating its role both in presence and absence of systemic inflammation (18) with Sensitivity / Specificity profile of 83.1% / 76.7 % compared with standard DNA method (18).). Out of 102 patients whose average daily intake was less than 50% of calculated requirement, those with reduced PAB had high mortality rate (19). In another study on hemodialysis patients, PAB was identified as a surrogate marker of malnutrition with 72% sensitivity at 29.5mg/dl cut off and significant correlation with other biochemical markers (like Albumin with r=0.805) of malnutrition (p< 0.005)(20). Strong correlation between TRA level and risk of malnutrition in our study indicate that it can be clinically relevant biomarker to assess risk of malnutrition during disease progression. There are reports with strong correlation between PAB and TRA (p=0.001) support its utility as nutritional indicator in patients on nutritional support (21).

Some studies propose correlation of visceral protein with severity of underlying disease rather than nutritional status (22). It occurs more during early active phase of disease during which any increase in their concentration is due to improvement in overall clinical state and not merely due to improved nutritional status (22,23). However, current study showed that it is a good marker of malnutrition risk in systemic inflammation. It is known that PAB has highest ratio of essential to non essential amino acids of any protein in the body, making it distinct marker of protein synthesis (24) . Thus, its level reflects protein intake during anabolic state of illness. It helps to identify patients requiring nutrition intervention to enhance their care in hospital (25). Thus, it is recommended that PAB and TRA should be made part of nutritional assessment protocol forpatients with acute and chronic illness (26), a finding that support our view.

CONCLUSION:

Our study concluded that level of PAB and TRA are significantly reduced in Pulmonary Tuberculosis due to Acute phase response and associated malnutrition. Prealbumin and Trasferrin can be employed as simple, inexpensive and reliable indicators or screening tool to indentify high mortality risk in patients and probalbility of relapse in PTB. However, in normal individuals they can be used to detect malnutrition, which is the major risk factor for occurrence of TB infection in vulnerable population for eg. in household contacts. Such individuals require nutrition intervention.

PAB alone may not be sufficient for nutritional assessment but should be a part of detailed nutritional protocol to assess malnutrition risk in Pulmonary Tuberculosis. In future, serial Prealbumin concentration can be incorporated for deciding nutritional regime of PTB patients and also monitoring therapeutic effect. It requires large scale studies to establish its clinical utility and effect on disease outcome.

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